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MUSCARINIC RECEPTOR ANTAGONISTS IN THE TREATMENT OF OVERACTIVE BLADDER

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ABSTRACT

A wealth of clinical evidence supports the view that muscarinic receptor antagonists are effective in the treatment of overactive bladder. However, treatment-limiting adverse effects such as dry mouth, constipation, and blurred vision have restricted the usefulness of previously available agents, such as oxybutynin. A real need therefore existed for effective and well-tolerated agents for the long-term management of the troublesome symptoms of overactive bladder. This review outlines the various approaches that have been used in attempts to overcome the tolerability problems of oxybutynin. It also describes how advances in our understanding of muscarinic receptors and bladder function has led to the potential development of either tissue- or subtype-selective antimuscarinic agents with improved tolerability. Drugs that have been developed in this way include tolterodine and darifenacin, each of which shows some bladder selectivity in animal models. Unlike darifenacin, however, the bladder selectivity of tolterodine has been confirmed by numerous clinical studies. Tolterodine's improved tolerability compared with oxybutynin, along with its equivalent therapeutic efficacy at recommended dosages, permits patients to experience the beneficial effects of long-term treatment. Tolterodine therefore represents a real alternative for the long-term management of overactive bladder. The results of ongoing clinical studies with darifenacin are awaited before it can be concluded that selective antagonism of M_3 receptors leads to improved tolerability over existing agents in the treatment of overactive bladder. Similarly, the potential improvements in tolerability associated with different dosage formulations of oxybutynin, and the clinical utility of *S*-oxybutynin, are yet to be conclusively demonstrated. UROLOGY **55** (Suppl 5A): 33–46, 2000. © 2000, Elsevier Science Inc.

Overactive bladder, which gives rise to the urinary symptoms of frequency, urgency, and urge incontinence, is a chronic and debilitating disease that has a profound effect on patients' quality of life.[1,2] It may affect as many as 50 million individuals in the developed world. The symptoms of overactive bladder are attributed to involuntary contractions of the detrusor muscle during bladder filling—so-called detrusor instability or hyperreflexia (the latter associated with neurologic disease).

It must be remembered that lower urinary tract symptoms are not disease-specific. While detrusor overactivity may be suspected in a patient with symptoms suggestive of overactive bladder, this needs to be confirmed on the basis of pressure–flow urodynamics. Nevertheless, empirical treatment on the basis of a clinical diagnosis of overactive bladder is an entirely acceptable practice. Invasive urodynamic investigation should be reserved for those patients who fail to respond to therapy.

Behavioral intervention is recommended by most authoritative guidelines,[3,4] but pharmacologic therapy remains the cornerstone of management for the majority of patients with overactive bladder. Of available agents, muscarinic receptor antagonists are the treatment of choice.[3] Historically, however, the utility of muscarinic receptor antagonists has been limited by poor tolerability as a result of frequent adverse events of an antimuscarinic nature.[5,6] Dry mouth (as a result of muscarinic receptor blockade in the salivary glands) is a particularly problematic adverse effect of these agents, and frequently leads to treatment discontinuation.

As overactive bladder follows a chronic course, requiring potentially lifelong therapy, the outlook for patients unable to tolerate existing antimuscarinic therapy has been poor. A real need therefore

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existed for effective and well-tolerated agents to manage the troublesome symptoms of overactive bladder in the long term.

The aim of this review is to discuss how advances in our understanding of muscarinic receptors and bladder function has led to the potential development of subtype- or tissue-selective compounds. These are predicted to have improved tolerability, while maintaining therapeutic efficacy, in patients with an overactive bladder. The review focuses on three antimuscarinic agents that are currently of interest: oxybutynin, tolterodine, and darifenacin.

RATIONALE FOR THE USE OF ANTIMUSCARINIC AGENTS IN OVERACTIVE BLADDER

The etiology of overactive bladder remains unknown, and may involve both neurologic and myogenic causes.[7,8] It is well established, however, that acetylcholine-induced stimulation of post-ganglionic muscarinic receptors on detrusor smooth muscle is involved in both normal and involuntary bladder contraction.[9] This profile explains the therapeutic efficacy of muscarinic receptor antagonists in overactive bladder.

Muscarinic receptors are heterogeneous in nature and widely distributed throughout the body. Five molecularly distinct subtypes are known to be exist (M_1–M_5), and tissues may contain a number of different subtypes[10] (Table I). The human urinary bladder smooth muscle, for example, contains a mixed population of M_2 and M_3 subtypes. The M_2 receptor is the predominant subtype in the bladder (about 80% of the total muscarinic receptor population),[11] but mediation of bladder contraction by the minor population of M_3 receptors is well documented.[12]

Stimulation of M_3 receptors by acetylcholine leads to phosphoinositol hydrolysis,[13] and ultimately to accumulation of intracellular calcium and smooth muscle contraction. However, there is an evolving role for the functional involvement of the M_2 receptor in bladder contraction in various species.[14,15] Activation of these receptors leads to inhibition of adenylate cyclase. This is thought to cause smooth muscle contraction by indirect inhibition of sympathetically (β-adrenoreceptor)-mediated augmentation of cyclic adenosine monophosphate (cAMP) levels and bladder relaxation.[14] During micturition, it has therefore been suggested that activation of M_3 receptors by acetylcholine evokes direct smooth muscle contraction, while stimulation of M_2 receptors reverses sympathetically mediated smooth muscle relaxation. The end result is more efficient voiding of urine.[12]

Other potential mechanisms for M_2-mediated bladder smooth muscle contraction include activation of nonspecific cation channels and stimulation of rho proteins (each yet to be demonstrated in urinary bladder), or inactivation of potassium channels.[12]

Antimuscarinic agents may not only interfere with the postjunctional effects of acetylcholine on the detrusor, but also with acetylcholine release from parasympathetic nerves. Indeed, presynaptic muscarinic receptors have been identified in various tissues, including the bladder. Activation of these receptors facilitates (M_1) or inhibits (M_2/M_4) the release of acetylcholine, according to the frequency of nerve stimulation.[16–22] It is thought that activation of presynaptic facilitating M_1 receptors may serve as an amplification mechanism during micturition, when intense parasympathetic activity occurs. In contrast, the inhibitory M_2/M_4 receptors appear to be preferentially activated at low frequencies of nerve stimulation.

It is clear that the muscarinic regulation of bladder function is a complex process. The relative functional role of the different pre- and postjunctional receptor subtypes in vivo, along with the interrelationships between these subtypes in terms of regulating bladder function, requires clarification (Figure 1). Thus, the optimal receptor selectivity profile of new antimuscarinic agents for overactive bladder is yet to be determined.

OXYBUTYNIN

Oxybutynin was originally identified in the 1960s as a potential treatment for gastrointestinal hypermotility.[23,24] Further investigation showed that it was effective in inhibiting uncontrolled bladder contractions.[25] Subsequently, oxybutynin became the most widely used pharmacologic agent for the treatment of overactive bladder.

PHARMACODYNAMICS

Radioligand binding studies indicate that oxybutynin is a potent muscarinic receptor antagonist with some degree of selectivity for M_3 and M_1 receptors over other muscarinic subtypes[26–29] (Table II). In human tissues, oxybutynin has higher affinity for muscarinic receptors in the parotid gland than in the bladder.[30,31] This leads to greater inhibition of electrically induced salivation than acetylcholine-induced bladder contraction in the anesthetized cat in vivo.[29] Functional studies in vitro show that oxybutynin competitively inhibits carbachol- and acetylcholine-induced contractions of isolated urinary bladder from various species[26,31,32–35] and electrically evoked contraction of guinea pig and human detrusor.[31,32,35]

These data are consistent with an antimuscarinic action of oxybutynin, though other mechanisms may contribute toward its therapeutic effect in

TABLE I. *Muscarinic receptor subtypes and their tissue distribution*

Receptor subtype	Location
M_1	Brain (cortex, hippocampus); glands; sympathetic ganglia
M_2	Heart; hindbrain; smooth muscle
M_3	Smooth muscle; glands; brain
M_4	Basal forebrain; striatum
M_5	Substantia nigra

Adapted from Caulfield & Birdsall.[10]

TABLE II. *In vitro affinity* of tolterodine, oxybutynin, and darifenacin for muscarinic receptor subtypes expressed in Chinese hamster ovary cells*

Receptor Subtype	Antagonist nmol/L		
	Tolterodine	Oxybutynin	Darifenacin
M_1	3.0	2.4	35.0
M_2	3.8	6.7	56.0
M_3	3.4	0.67	1.2
M_4	5.0	2.0	18.0
M_5	3.4	11.0	9.0

* *Expressed as the mean dissociation constant,* K_i. *Low values indicate high affinity at that particular receptor subtype.*
Adapted from Gillberg et al.,[15] *and Nilvebrant et al.*[29]

vivo.[36] For example, a direct spasmolytic action on bladder smooth muscle, thought to be mediated by calcium antagonism,[33,37–40] along with possible local anesthetic effects have been reported.[39,41] However, the spasmolytic/local anesthetic effects of oxybutynin occur at much higher concentrations than its antimuscarinic actions (micromolar and nanomolar, respectively).[33,37–40] Because of this, it is generally accepted that the clinical effects of oxybutynin occur solely through muscarinic blockade,[31] as therapeutically relevant plasma concentrations are within the nanomolar range.[42]

Clinical Studies

The clinical efficacy of oxybutynin for the treatment of overactive bladder is well documented.[5] Although diverse in terms of their outcome measures, most studies show that oxybutynin is more effective than placebo.[43–50] Moreover, comparative studies show that oxybutynin is at least as effective as propantheline,[47,51,52] propiverine,[50] penthienate,[53] and trospium.[54,55]

In the largest of these studies, Madersbacher *et al.*[50] treated 366 overactive bladder patients randomized to treatment with 5 mg oxybutynin three times a day (n = 145), 15 mg propiverine three times a day (n = 149), or placebo (n = 72) for 28 days. Urodynamic assessment showed significant, comparable increases in bladder capacity at normal desire to void and maximum cystometric capacity following oxybutynin and propiverine treatment. About 80% of patients in each drug group reported global symptomatic improvement.

Although oxybutynin is clinically effective, it causes dose-related antimuscarinic adverse effects (particularly dry mouth, but also constipation, drowsiness, and blurred vision). These are deleterious, and often lead to poor patient compliance, treatment discontinuation, or dose reduction to a level of minimal clinical benefit. This is exemplified in the findings of a short follow-up study of 231 patients receiving antimuscarinic therapy for overactive bladder, 84% of whom were treated

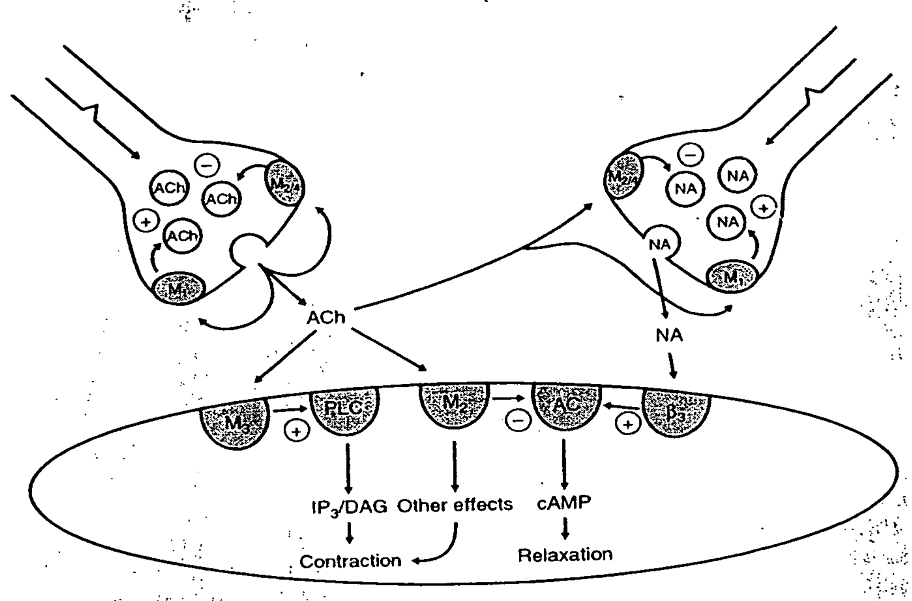

FIGURE 1. *Schematic representation of pre- and postjunctional muscarinic receptor subtypes in the urinary bladder; AC = adenylate cyclase; ACh = acetylcholine; cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol;* IP_3 *= inositol 1,4,5-trisphosphate; NA = noradrenaline; PLC = phospholipase C.*

with oxybutynin. At 6 months, only a minority of patients were still being treated. The most common reason for discontinuation was adverse effects.[6]

Dry mouth can be expected in at least 50% of patients treated with oxybutynin. In combination with other antimuscarinic adverse effects, it may be sufficiently severe to warrant treatment discontinuation in up to 27% of patients.[5] In routine clinical practice, this figure may be considerably higher. The clinical benefits of oxybutynin are therefore often far outweighed by its poor tolerability profile. This means that many patients are deprived of effective long-term treatment for their overactive bladder symptoms.

A number of approaches have been investigated as potential ways of improving the tolerability of oxybutynin. These are discussed in the following sections.

NEW APPROACHES TO IMPROVE TOLERABILITY

New approaches to improving the tolerability of oxybutynin include alternative routes of administration, use of extended-release oral formulation technology, and stimulation of salivation. Clinical development of the *S*-enantiomer of oxybutynin has also been advocated.

Alternative Routes of Administration

The antimuscarinic activity of oxybutynin resides in both the parent drug and its major metabolite, *N*-desethyl oxybutynin.[31,46] Following oral administration, levels of the metabolite are some sixfold higher compared with parent oxybutynin. This is thought to give rise to the adverse effects. Reducing the extent of first-pass metabolism or the rate of absorption should therefore result in lower levels of the metabolite, which may lead to improved tolerability. Two approaches have been investigated in this context: intravesical instillation and rectal administration.

Intravesical Instillation. Numerous studies have evaluated the efficacy and tolerability of intravesical instillation of oxybutynin.[56–64] Therapeutically, the effect of intravesical oxybutynin is deemed to be systemic rather than topical, as cystometric effects take 2 hours to occur.[65] Other studies, however, report a more rapid onset of action.[64]

Marked improvements in tolerability have been observed with intravesical oxybutynin compared with oral administration.[57,58,60,63] This can be partly attributed to the fact that the drug does not have to pass through the portal system before it reaches the systemic circulation.[59] Consequentially, first-pass metabolism is reduced, as shown by decreased systemic exposure to *N*-desethyl oxybutynin following intravesical administration, compared with the oral route.[63] Some metabolism to *N*-desethyl oxybutynin does occur, which probably accounts for the adverse effects in certain patients.

For those unable to tolerate oral therapy, intravesical application of oxybutynin may be an aid to improving tolerability. The problem is that this form of treatment is unacceptable to most patients. It is also expensive, and requires full manual dexterity on the part of the patient. Intravesical instillation of oxybutynin is therefore only of likely benefit, by improved tolerability, to those patients already using clean intermittent catheterization (CIC) because of voiding difficulties. Suitable candidates include patients with spinal injury, myelodysplasia, or multiple sclerosis.

Rectal Administration. It is likely that rectal administration of oxybutynin may mimic the systemic effects of intravesical instillation, and so represent a more acceptable means of administration in patients unable to tolerate oral therapy.

Relatively few studies have determined the efficacy and tolerability of rectal oxybutynin compared with oral administration. In a small pharmacokinetic study in healthy volunteers, Collas and Malone-Lee[66] reported slower absorption of oxybutynin after rectal administration, with relatively constant levels for at least 12 hours postdose. Production of the *N*-desethyl metabolite was also slowed among those who received rectal oxybutynin, with decreased systemic exposure compared with oral administration of an identical dose. This led to a decreased frequency and severity of adverse events.

Similarly, a small study in female overactive bladder patients unable to tolerate oral antimuscarinic therapy reported an improvement in tolerability during treatment with oxybutynin rectal suppositories. Thirty-six percent of patients reported a >50% improvement in subjective symptoms.[67] Rectal administration of oxybutynin may therefore be an alternative way of improving the tolerability of oxybutynin, and further studies are warranted. It is important to consider, however, that country-specific differences exist in the acceptability of rectal drug administration.

Extended-release Oral Formulations

Extended-release, once-daily formulations of oxybutynin have been developed. These reduce concentration-dependent antimuscarinic adverse events and improve patient convenience. One formulation is based on the OROS osmotic drug delivery system (ALZA Corp., Palo Alto, CA), which releases the drug at a controlled rate over 24 hours.

Pharmacokinetic investigations in healthy volunteers show that this extended-release formula-

tion of oxybutynin has a smoother plasma concentration–time profile. This overcomes the marked peak-to-trough fluctuations in plasma levels of both oxybutynin and its *N*-desethyl metabolite that occur with thrice daily immediate-release oxybutynin.[68] Gupta and Sathyan[68] found a trend toward a lower incidence of dry mouth with the extended-release formulation (though no assessment of severity was reported). The authors attributed this to reduced first-pass metabolism (ie, reduced metabolite exposure) and to maintenance of lower and less fluctuating plasma levels.

Subsequent clinical trials in patients with overactive bladder show that the extended-release formulation of oxybutynin has comparable efficacy to immediate-release oxybutynin.[69] Dry mouth was the most frequently reported adverse event during treatment with extended-release oxybutynin, followed by constipation (13.1%) and somnolence (11.9%).[70] Studies have indicated that the incidence of troublesome dry mouth (moderate–severe intensity) in patients treated with extended-release oxybutynin was reduced by about 50% compared with those receiving the immediate-release formulation in one double-blind study (24.5% versus 46%; $P = 0.03$).[71]

In a placebo-controlled study,[72] both the extended-release and immediate-release formulations of oxybutynin caused significantly higher incidence of dry mouth compared with placebo. Fewer patients treated with extended-release oxybutynin reported dry mouth compared with those taking the conventional formulation.[72] These data support the results of an earlier, open-label study.[73] Moreover, a multicenter, prospective trial has demonstrated that many patients are able to tolerate a higher dosage of extended-release oxybutynin than of the immediate release formulation.[74]

In addition to the OROS osmotic drug delivery system, other formulations are available that provide an extended duration of drug release, and so permit once-daily administration of oxybutynin. Birns *et al.*[75] reported the efficacy and tolerability of an extended-release 10-mg tablet, given once daily, compared with conventional oxybutynin, 5 mg twice daily, in 128 patients with overactive bladder. While the results showed comparable efficacy for the two formulations, the extended-release formulation was better tolerated, with patients reporting only half the total number of adverse events compared with those treated with the conventional formulation.

In contrast, another study in a much smaller number of patients failed to demonstrate improved tolerability for the extended-release formulation. Nilsson *et al.* recorded a similar frequency of dry mouth to that reported for conventional oxybutynin.[76]

The results of studies with once-daily, extended-release formulations of oxybutynin generally demonstrate efficacy, but fail to provide conclusive evidence of improved tolerability.[77] Further studies of longer duration have been called for in order to confirm the apparent improvement in tolerability. In particular, the decreased incidence and severity of dry mouth associated with the OROS extended-release formulation of oxybutynin[78] requires replication.

A particular criticism of the trials with the extended-release formulation of oxybutynin reported to date is that the patient group selected might not be representative of the population at large. While this criticism can be applied to most pharmaceutical trials in this area, certainly, some of the data reported are based on patients who have previously been on oxybutynin and have responded to it, and there is the risk therefore that a responder analysis is in fact being carried out. This needs to be addressed in future work with this compound. Indeed, all drug trials with agents being tested on the overactive bladder should aim to investigate patients being treated at the community level to avoid the bias produced by selecting patients who either failed other anticholinergic therapy or responded to it and who are now being included in a trial because they happen to be available in the clinic and willing to participate.

Stimulation of Salivation

An interesting approach to overcoming the tolerability problems of oxybutynin has recently been reported by Hooper and colleagues.[79] They evaluated the efficacy of salivary stimulant pastilles, to be chewed as required for dry mouth, as an adjunct to oxybutynin therapy. The results of this small pilot study in 30 women with overactive bladder indicate no effect on the frequency of dry mouth during oxybutynin therapy, but significantly reduced severity of this troublesome side effect. There was also preliminary evidence to suggest that this approach allowed patients to tolerate higher doses of oxybutynin (up to 5 mg three times a day), which may translate into improved therapeutic benefits. However, the long-term patient acceptability of chewing up to 12 pastilles/day needs to be determined.

The role of salivary stimulants and artificial saliva to counteract dry mouth associated with oxybutynin therapy, along with their potential to permit the use of higher (more effective) dosages of oxybutynin, requires further investigation in larger controlled studies.

S-Oxybutynin

Structurally, oxybutynin contains a chiral center and therefore exists as two enantiomeric forms.

Clinically, however, the racemate is used. Several studies have established that the antimuscarinic component of the drug's pharmacologic action is stereoselective, with the *S*-enantiomer showing weaker antimuscarinic activity than *R*-oxybutynin or the racemate.[28,33,40,80] The spasmolytic action of oxybutynin is, however, not subject to stereoselectivity.[28,40,80] This suggests that *S*-oxybutynin may represent an improvement over the racemate—spasmolytic activity would be retained, but the tendency to block antimuscarinic receptors would be reduced, therefore decreasing side effects.

The drawback, of course, is that the spasmolytic effects of oxybutynin may contribute to the therapeutic response in vivo. In comparative terms, however, the concentration of oxybutynin required for a spasmolytic effect in vitro is far higher than that associated with the antimuscarinic effect. For example, *S*-oxybutynin had a median inhibitory concentration (IC_{50}) of 14 μmol/L for inhibition of potassium-induced contractions in guinea pig isolated bladder (spasmolytic effect), whereas the K_B value for inhibition of carbachol-induced contraction (antimuscarinic effect) was some 25 times lower (0.56 μmol/L).[33]

These findings suggest that the spasmolytic action of oxybutynin may not be clinically relevant at the recommended dosages. Thus, while pharmacokinetic studies in healthy volunteers showed that oral doses of *S*-oxybutynin of up to 320 mg did not give rise to the antimuscarinic adverse effects of racemic oxybutynin,[81] the efficacy, safety and tolerability of *S*-oxybutynin in patients with overactive bladder has yet to be reported.

TOLTERODINE

Tolterodine is the first drug to have been specifically developed for the treatment of patients with overactive bladder presenting with frequency, urgency, and urge incontinence. Given the complexity of the role of muscarinic receptors in bladder function, this agent was developed using a functional approach to achieve bladder selectivity, rather than relying on muscarinic receptor subtype selectivity.

Pharmacodynamics

Tolterodine is a potent, competitive muscarinic receptor antagonist[29,35,82] that demonstrates high affinity for muscarinic receptors, in the absence of selectivity for any particular muscarinic receptor subtype (M_1–M_5)[29,82] (Table II). The major active 5-hydroxymethyl metabolite of tolterodine (PNU-200577; labcode DD 01) exhibits a similar pharmacologic profile.[83] This is in contrast to oxybutynin, which shows increased selectivity for M_3 and M_1 receptors over other muscarinic subtypes.[26–29]

In functional studies in vitro, tolterodine is as potent as oxybutynin in inhibiting carbachol-induced contractions of guinea pig detrusor muscle and human bladder[29,35] (Table III). Similar findings were reported in a study using bladder samples from patients with cystometrically confirmed overactive bladder. In that study, tolterodine and oxybutynin inhibited electrically induced contractions with mean IC_{50} values of 2.5 and 3.2 nmol/L, respectively.[84] These values are in close agreement with the affinity of tolterodine and oxybutynin for muscarinic receptors in guinea pig detrusor muscle, as determined by functional and radioligand binding studies (Table III). However, in guinea pig parotid glands (which contain a homogeneous population of M_3 receptors), tolterodine has an 8-fold lower affinity than oxybutynin for muscarinic receptors. This accords with the affinity of these agents for M_3 receptors expressed in Chinese hamster ovary cells (K_i 3.4 and 0.67 nmol/L, respectively).[29,82]

These in vitro results were the first indication that tolterodine demonstrates "bladder selectivity," a finding that was subsequently confirmed in the anesthetized cat model.[29,82] In these studies, tolterodine showed a more pronounced effect on acetylcholine-induced bladder contraction than on electrically induced salivation. In contrast, oxybutynin showed the opposite tissue selectivity profile (Table IV). Thus, while the dose–response curves for inhibition of bladder contraction were similar for tolterodine and oxybutynin, the former drug was a much less potent inhibitor of salivation (Figure 2).

These results indicate that selectivity for M_3 receptors over other subtypes is not necessary for effective inhibition of bladder contraction in vivo, and may result in more pronounced effects on salivation. Indeed, darifenacin, which is selective for the M_3 receptor subtype, was a significantly more potent inhibitor of salivation than bladder contraction at high doses.[15]

Such findings suggest either that M_3 receptors in glands are more sensitive to blockade than those in the bladder, or that M_3 receptors are heterogeneous.[85,86] Alternatively, the data could suggest a role for M_2 receptors in bladder contraction, and that blockade of these receptors contributes to the favorable tissue selectivity profile of tolterodine. While the mechanism responsible for the bladder-selective effect of tolterodine remains to be elucidated, it is clear that the findings for oxybutynin in the anesthetized cat are analogous to clinical experience with this agent.[5]

Evidence of Bladder Selectivity in Humans

Based on preclinical research, tolterodine was expected to show improved tolerability compared

TABLE III. ***Affinity* of tolterodine, oxybutynin and darifenacin for muscarinic receptors in functional and radioligand binding studies in vitro***

	Functional Data, K_B (nmol/L)		Binding Data, K_i (nmol/L)			
	Urinary bladder		Urinary bladder		Parotid, M_3	Heart, M_2
Antagonist	Human	Guinea Pig	Human	Guinea Pig	Guinea Pig	Guinea Pig
Tolterodine	4.0	3.0	3.3	2.7	4.8	1.6
Oxybutynin	—	4.4	4.5	4.0	0.62	2.8
Darifenacin	—	0.87	—	78.0	1.7	44.0

* *Expressed as the mean dissociation constants K_B and K_i. Low values indicate high affinity at muscarinic receptors in the particular tissue.*
Adapted from Gillberg et al.,[15] *and Nilvebrant et al.*[29]

TABLE IV. ***Mean ID_{50} values, along with in vitro affinity ratios, of tolterodine, oxybutynin, and darifenacin in inhibiting acetylcholine-induced urinary bladder contraction and electrically evoked salivation in the anesthetized cat***

	ID_{50} (nmol/kg)		Affinity Ratios	
Antagonist	Bladder Contraction	Salivation	Bladder: Parotid Gland	M_2:M_3
Tolterodine	101*	257	0.56	1.1
Oxybutynin	200*	104	6.5	10.0
Darifenacin	119	99.0	46.0	47.0

* *Calculated from K_i values in guinea pig tissues (bladder:parotid gland) and Chinese hamster ovary cells (M_2:M_3).* * *$P < 0.05$ versus effect on salivation.*
Adapted from Gillberg et al.,[15] *and Nilvebrant et al.*[29]

with oxybutynin in the clinical setting. Two early studies evaluated the antimuscarinic profile of tolterodine in healthy human volunteers. Both studies showed that the pharmacologic (ie, antimuscarinic) effect of tolterodine was rapid, occurring within 1 hour of oral administration.[87,88]

In their single-dose study, for example, Brynne *et al.*[88] reported dose-dependent inhibition of bladder function (as evinced by micturition difficulties) that persisted for up to 16 hours postdose at the highest dose studied (12.8 mg). While stimulated salivation was also decreased at this dose level, the effect was only apparent around the time of peak serum levels, and was shorter in duration than the effect on the bladder.

This was the first evidence of tolterodine's selectivity for the bladder over salivary glands in humans, a finding that was confirmed by the cystometric study of Stahl and colleagues.[87] In that study, a sustained inhibitory effect on bladder function persisted for up to 5 hours following a single oral dose of 6.4 mg tolterodine. Stimulated salivation was also inhibited, but only around the time of peak serum levels. No effects on blood pressure or heart rate were observed at doses up to 6.4 mg,[87,88] though this dose was found markedly to increase residual urinary volume.[87] Given that an increase in residual urinary volume increases the risk of urinary retention, the maximum dosage later studied in the phase II program was therefore 4 mg twice a day.[82]

Clinical Studies

The clinical efficacy and tolerability of tolterodine has been evaluated in 12 double-blind, randomized, parallel-group studies in which >1,600 overactive bladder patients received tolterodine, 0.5–4 mg twice daily, for up to 12 weeks.[89] All but one study included a placebo treatment arm, and in three cases oxybutynin was used as a comparator agent.

Early phase II studies aimed to determine the optimal dose range and safety/tolerability of tolterodine, administered at dosages of 0.5, 1, 2, and 4 mg twice daily for 2 weeks[90–92] (data on file, Pharmacia & Upjohn). Pooled analysis of these studies, which included a total of 319 patients, showed that tolterodine was well tolerated and evoked a consistent, dose-related reduction in micturition frequency and urge incontinence episodes. The optimal dosage was deemed to be 1–2 mg twice a day.[93]

Subsequent phase III studies compared tolterodine, 2 mg twice a day, with oxybutynin, 5 mg three times a day.[94–96] Dosage reduction was permitted in the case of intolerable adverse events. All studies were of 12 weeks' duration and used virtually the

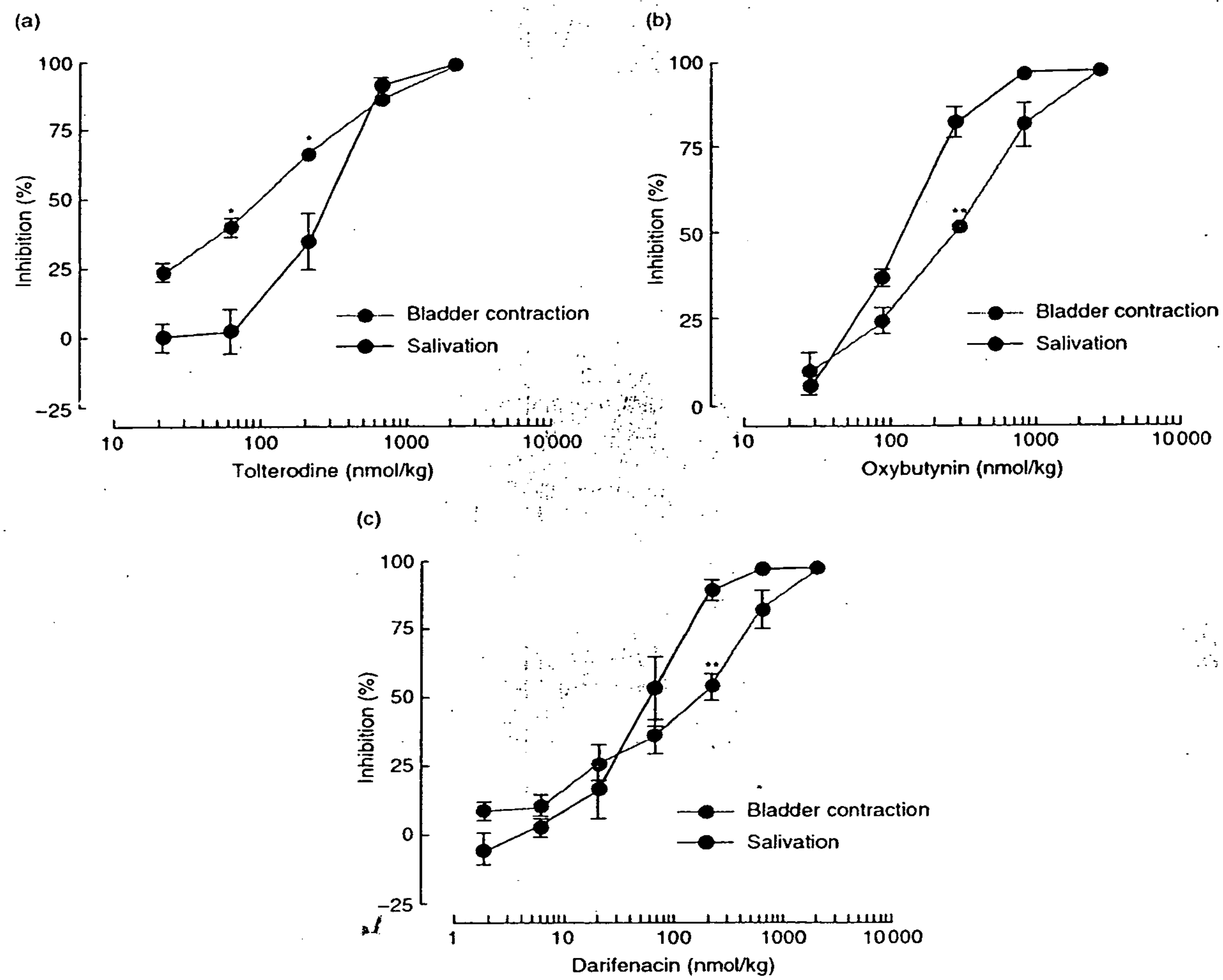

FIGURE 2. *Effect of (a) tolterodine, (b) oxybutynin, and (c) darifenacin on mean (± SEM) bladder contraction and salivation in the anesthetized cat;* $^{*}P < 0.05$, $^{**}P < 0.01$ *versus effect on salivation. Reprinted from Gillberg* et al.[15] *and Nilvebrant* et al.[29] *©1998 and 1997, respectively; with permission from Elsevier Science.*

same protocol, which permitted data pooling and a global analysis of efficacy.[97]

Overall, tolterodine was of equivalent therapeutic efficacy to oxybutynin. Micturition frequency and urge incontinence episodes were decreased, while volume voided during micturition was increased, to a similar extent in each treatment group (Figure 3).

These changes were clinically relevant to patients, as improvements in patient perception of bladder symptoms were also apparent. Thus, when asked to evaluate their bladder symptoms on a 6-point scale (0 = no problems; 5 = severe problems), 52% of patients treated with tolterodine reported an improvement in score (defined as a decrease in score of ≥1 point) after 12 weeks' treatment, compared with 39% of placebo recipients and 50% of those receiving oxybutynin.[97]

The major finding of interest in these studies was that tolterodine was better tolerated than oxybutynin. There was a lower incidence and severity of dry mouth (Figure 4), less need for dosage reduction, and fewer treatment withdrawals. For example, the overall incidence of dry mouth among tolterodine, oxybutynin, and placebo recipients was 39%, 78%, and 16%, respectively.[97] Troublesome dry mouth (moderate–severe intensity) was reported by 60% of oxybutynin-treated patients, compared with only 17% of those taking tolterodine. This explains the significantly lower frequency of dosage reduction among tolterodine recipients (9% versus 32% of those receiving oxybutynin; $P = 0.001$). Interestingly, patients who changed to a lower dosage of oxybutynin continued to report a higher frequency of adverse events, along with a higher frequency and intensity

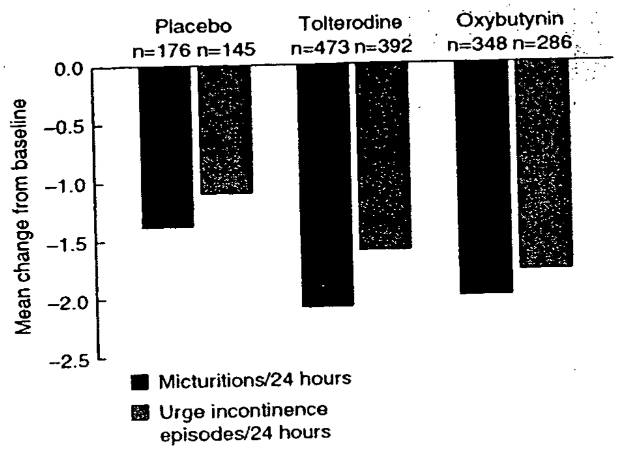

FIGURE 3. *Effect of tolterodine (2 mg twice daily) versus oxybutynin (5 mg three times daily) and placebo on micturition diary variables after 12 weeks' treatment; data shown is mean change from baseline in a global analysis of 4 phase III studies in patients with overactive bladder. Adapted from Van Kerrebroeck* et al.,[94] *Abrams* et al.,[95] *and Drutz* et al.[96]

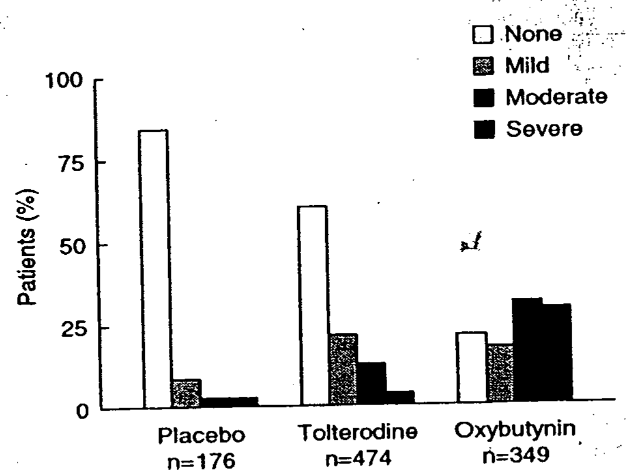

FIGURE 4. *Global analysis of the incidence and intensity of dry mouth during 12 weeks' treatment with tolterodine (2 mg twice daily), oxybutynin (5 mg three times daily), or placebo in four phase III studies in patients with overactive bladder. Adapted from Van Kerrebroeck* et al.,[94] *Abrams* et al.,[95] *and Drutz* et al.[96]

of dry mouth, than those maintained with 2 mg tolterodine twice a day. Although no direct comparative trials have been conducted, the adverse events profile of tolterodine also compares favorably to that of extended-release oxybutynin. In addition to the lower overall incidence of dry mouth (39.5% versus 60.8%), tolterodine is associated with a lower incidence of constipation (6.5% versus 13.1%) and somnolence (3.8% versus 11.9%) than the extended release formulation.[70,98] The lower incidence of cognitive adverse events during tolterodine treatment may be explained by its low lipophilicity and poor penetration into the central nervous system.[99]

One potential criticism of the comparative tolterodine studies is that oxybutynin is frequently prescribed at initial dosages lower than 5 mg three times a day. A study was therefore performed that compared tolterodine (2 mg twice a day) with a more naturalistic approach to oxybutynin therapy, where treatment was started at a dosage of 2.5 mg twice a day, increasing to 5 mg twice a day after 2 weeks, in patients aged ≥50 years. Patients could revert to the lower dosage of oxybutynin if unacceptable adverse events occurred, while the dosage of tolterodine was maintained at 2 mg twice daily throughout. A total of 378 patients with overactive bladder were included. After 10 weeks' treatment, relief of overactive bladder symptoms was comparable in the two treatment groups, though tolterodine was associated with better tolerability.[100]

These data show that the favorable tolerability of tolterodine permits the optimal dosage of 2 mg twice daily to be used, whereas some patients taking oxybutynin may receive suboptimal therapy if effective dosages cannot be tolerated.

The continued efficacy and tolerability of tolterodine has since been confirmed in long-term open-label studies of 9–12 months' duration.[101–103] For example, 512 of 815 patients (63%) completed 12 months' treatment, during which the therapeutic efficacy of tolterodine was maintained. Few patients discontinued therapy because of troublesome dry mouth (3%) or adverse events generally (15%).[101] Similar findings were reported for a group of 854 patients offered open-label treatment for up to 9 months.[102] These outcomes compare very favorably to long-term treatment with existing antimuscarinic agents (primarily oxybutynin).[6] In Kellehér *et al.*'s follow-up study[6] 82% of patients had discontinued treatment by 6 months.

Overall, the findings of the clinical program confirm that tolterodine is an effective new agent with excellent safety and tolerability for the long-term treatment of overactive bladder.

DARIFENACIN

Given the major involvement of M_3 receptors in bladder contraction,[12] compounds selective for this subtype may prove effective in the treatment of overactive bladder without the systemic adverse effects caused by blockade of M_1 and M_2 receptors.[104] Darifenacin is a new agent, currently undergoing clinical trials, that was identified for development by using this subtype-selectivity rationale.

PHARMACODYNAMICS

Darifenacin has been shown to exhibit M_3 receptor selectivity, using radioligand binding and functional studies in vitro[15,105–107] (Tables II and III). Specifically, this agent has at least an 11-fold higher affinity for M_3 receptors than for the M_2 subtype.[106–108] Its selectivity has been confirmed in functional in vitro studies that demonstrated the greater potency of darifenacin in inhibiting agonist-induced contractions of the guinea pig ileum and bladder (M_3) than of the atria (M_2).[105]

Further evidence for antagonism of M_3 receptors comes from studies in which accumulation of total inositol phosphates in human detrusor muscle cells, in response to stimulation of M_3 receptors by carbachol, was decreased by darifenacin.[109] Interestingly, while darifenacin is of similar potency to atropine for inhibition of acetylcholine-induced contraction of guinea pig urinary bladder, it shows a 5-fold lower affinity for muscarinic receptors in the parotid gland.[105]

Subsequent in vitro functional studies show that darifenacin is less potent than atropine for inhibition of carbachol-stimulated ^{86}Rb efflux from guinea pig submandibular gland.[110] These findings provide tentative evidence of the possible selectivity of darifenacin for muscarinic receptors in the bladder over those in the salivary glands. Similar selectivity has also been reported for zamifenacin.[111]

One possible explanation for this selectivity is heterogeneity among M_3 receptors,[85,86] though to date only one M_3 receptor has been identified using molecular sequencing.[10] In an anesthetized dog model, for example, darifenacin showed 8.6 times greater potency in inhibiting pelvic nerve–stimulated bladder contractions than trigeminal nerve–stimulated salivation. No effects on heart rate were observed.[112] Selectivity for the bladder over salivary glands was also apparent for both oxybutynin and tolterodine, albeit less pronounced (3.6-fold and 5.1-fold, respectively).[112] Cystometric studies in both the conscious and anesthetized rat provide some evidence of a more pronounced effect for darifenacin on the bladder compared with salivation, relative to that observed for oxybutynin.[113,114]

Such findings contrast with those obtained in an anesthetized cat model.[15,29] In those studies both darifenacin and oxybutynin showed greater potency in inhibiting nerve-stimulated salivation than acetylcholine-induced bladder contraction; only tolterodine showed bladder selectivity (Table IV, Figure 2).

It is difficult to explain these contrasting findings, other than by an argument based on differences in tissue selectivity according to the animal model used. However, the bladder selectivity of tolterodine in animal models is also apparent in humans, while the reported profile for oxybutynin mirrors clinical experience with this agent. Indeed, as previously discussed, tolterodine is as effective as oxybutynin for the treatment of overactive bladder, but has a much lower incidence and reported severity of dry mouth.[97] Whether the apparent bladder selectivity of darifenacin will also lead to improved tolerability in vivo relative to existing antimuscarinic agents remains to be established. In addition to development for an overactive bladder indication, research has been performed to determine the potential of darifenacin as an agent for irritable bowel syndrome. This research, based on the involvement of M_3 receptors in gut motility, shows that darifenacin is as potent as atropine for inhibiting agonist-induced contractions of the guinea pig ileum.[105] Moreover, darifenacin is a potent inhibitor of food- or cholecystokinin octapeptide–induced jejunal motility at doses lower than those inhibiting salivation.[115,116] Effects of darifenacin on rabbit iris smooth muscle have also been noted,[117] which is consistent with a role for M_3 receptors in the control of pupil size. Interestingly, darifenacin was more potent that oxybutynin in this regard.[117] Whether these effects of darifenacin will result in an increased propensity to cause constipation and blurred vision in the clinical setting, which are frequent dose-limiting adverse effects of oxybutynin, requires further investigation.

CLINICAL STUDIES

One small placebo-controlled study in 18 overactive bladder patients demonstrated improvements in urodynamic parameters following single oral doses of 10 mg darifenacin, though significant reductions in salivary flow were also apparent. No effects on salivation occurred at a dose of 2.5 mg, but this dose was no more effective than placebo, as measured by changes in urodynamic parameters.[118]

Dose-ranging studies are clearly required to determine the optimal dosage of darifenacin in terms of efficacy and tolerability. While one study has reported the effects of darifenacin, 7.5–30 mg/day, on generic and disease-specific quality-of-life parameters in overactive bladder patients, no tolerability data were provided.[119] Few clinical data are therefore available to support the hypothesis that selective M_3 antagonism with darifenacin will confer improved tolerability in the treatment of overactive bladder. The results of ongoing studies will be required before firm conclusions can be drawn.

CONCLUSIONS

There is little doubt that compounds with antimuscarinic properties are effective in the treatment of overactive bladder, and so form the mainstay of

treatment for this common and distressing condition. However, the usefulness of previously available agents, such as oxybutynin, has been limited by the occurrence of treatment-limiting adverse events, principally dry mouth. Intravesical instillation of oxybutynin overcomes many of the tolerability problems associated with oral therapy, but this technique is not acceptable for the majority of patients with overactive bladder.

Recent research has focused on the use of different formulations (eg, extended-release tablet, rectal suppository) as a potential way of overcoming the tolerability problems of oxybutynin. Indeed, extended-release formulations of oxybutynin are now commercially available, though there is little evidence to support an improved tolerability profile compared with immediate-release oxybutynin.

S-Oxybutynin, which has weaker antimuscarinic activity than the racemate currently in clinical use, has shown favorable tolerability in early clinical studies, though the pharmacologic basis for its development remains controversial.

An alternative approach to improving the tolerability of antimuscarinic therapy for overactive bladder focuses on agents that show greater selectivity for the bladder (eg, tolterodine), and those that show selectivity for the muscarinic M_3 receptors involved in bladder contraction (eg, darifenacin). The bladder selectivity of tolterodine, which has been consistently demonstrated in preclinical and clinical studies, confers improved tolerability compared with oxybutynin, thereby allowing patients to continue to experience the beneficial effects of treatment in the long term.

As tolterodine is not selective for any particular muscarinic receptor subtype, selectivity for M_3 receptors does not seem to be a prerequisite for effective inhibition of bladder contraction in vivo. Rather, selectivity for M_3 receptors, as shown by darifenacin, may result in more pronounced dry mouth, as blockade of these receptors inhibits salivation. M_3 receptors are also involved in gut motility and visual accommodation, which suggests that M_3 selectivity could cause constipation and blurred vision. Such adverse effects are common during oxybutynin therapy. The results of ongoing clinical studies with darifenacin are awaited before it can be concluded that selective antagonism of M_3 receptors leads to improved tolerability over existing agents in the treatment of overactive bladder. In summary, the potential improvements in tolerability of antimuscarinic therapy conferred by the M_3 selectivity of darifenacin, or by different dosage formulations of oxybutynin, have yet to be conclusively demonstrated in the clinical setting. In contrast, the improved tolerability of tolterodine in comparative clinical studies, coupled with effective control of bladder symptoms, indicates that this agent is a real alternative for the long-term management of overactive bladder.

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